REMARKS

Claims 92, 129, 132, and 133 are pending. Claims 92, 132, and 133 are rejected under 35 U.S.C. § 112, first paragraph, as failing to meet the written description requirement, and claims 132 and 133 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 92, 129, 132, and 133 are rejected under 35 U.S.C. § 112, first paragraph, lacking enablement over the full scope of the claims and under 35 U.S.C. § 102(b) for anticipation over Tang et al. (WO 01/57190). Each of these rejections is addressed in turn below.

Amendments to the specification

The specification has been amended to include SEQ ID NO:60. The sequence comprises the fully conserved residues of Figure 3a at the positions specified in the figure. The sequence is described in the application on page 26, lines 28-29 :"A variant NsG33 at corresponding positions comprises the residues marked in Figure 3a as fully conserved (*)." X has been inserted at the positions where the amino acids are not fully conserved. No new matter is added by this amendment

Amendments to the claims

Claims 92 and 132 have been amended to specify that the protein is neurotrophic. Support for this can be found throughout the specification and in particular on page 71, first paragraph. Claims 92 and 132 have been further amended to specify that the treatment involves providing trophic support to striatal neurons by administering the polypeptide to the striatum. On page 41, lines 18-20, it is described that, in Huntington's disease, striatal neurons are affected. On page 50, lines 8-20, it is described that NsG33 is preferably applied to the striatum. Example 15 describes a neurotrophic (neuroprotection/neurogenesis) effect on striatal neurons. In the passage on page 70, lines 20, to page 71, line 8, it is described that this neurotrophic effect is trophic support.

Claims 132 and 133 have been amended by specifying that the fully conserved and strongly conserved residues are those marked in Figure 3a with "*" and ":" respectively. This is described in the figure legend to Figure 3a.

New claim 136 specifies that the neurotrophic polypeptide is capable of protecting striatal neurons against degeneration. This finds basis in, e.g., example 15.

New claim 134 is similar to claim 92, but the neurotrophic polypeptide is required to comprise a recited consensus sequence. The sequence comprises the fully conserved residues of Figure 3a at the positions specified in the figure. The sequence is described in the application on page 26, lines 28-29 ("A variant NsG33 at corresponding positions comprises the residues marked in Figure 3a as fully conserved (*)." X has been inserted at the positions where the amino acids are not fully conserved.

New claim 135 is filed with similar limitations to the polypeptide as in claim 134.

No new matter has been added by the present amendments.

Rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 92, 132, and 133 are rejected for failing to comply with the written description requirement. The Office contends that the claims do not recite a structure-function relationship. Applicant respectfully disagrees.

The claims filed herewith all recite a function of the protein used to treat Huntington's disease or used to provide trophic support to striatal neurons. The claims also recite a structure with a finite number of possible variations. Specifically, each claim recites the following structural features:

Claim 92: 95 % sequence identity to SEQ ID NO: 4 with conserved cysteines at specific positions.

Claims 132, 134, and 135: 95% sequence identity so SEQ ID NO: 4 with the position and identity of approximately 80% of the amino acids of SEQ ID NO: 4.

According to claim 92, only 5% of the amino acids can vary compared to the reference sequence, SEQ ID NO: 4. 5% of the amino acids correspond to 13 amino acids. In addition, it is specified that the 10 conserved cysteines cannot be varied. According to claims 132, 134, and 135, only 13 of the amino acids (5%) can be varied. Furthermore, it is specified that approximately 216 of the positions cannot be varied.

The specification discloses three proteins having the required function, SEQ ID NOs: 4, 9, and 14, which correspond to NsG33 sequences without signal peptide from human, mouse, and rat. These sequences are aligned in Figure 3a.

The percent sequence identity of the disclosed mouse and rat sequences to the human sequence is 81.9 and 79.6% respectively (page 80, Table 2). As the three different polypeptides are bioactive, the person of skill in the art would have understood that up to 20% of the amino acid residues in the human sequence can be varied without destroying the bioactivity. From the alignment in Figure 3a, the person of skill in the art is also given extensive guidance regarding which positions can be varied and which cannot be varied. First and foremost, the specification and the alignment identify the conserved cysteines, which may be involved in determining the three-dimensional structure of the bioactive protein. As recited in all independent claims, the conserved cysteines cannot be varied.

Furthermore, the person of skill in the art is informed that the residues which are conserved among the human, mouse, and rat sequences are residues that can probably not be

varied without affecting bioactivity. Accordingly, claims 132, 134, and 135 recite that these residues are conserved.

Finally, guidance is given in the specification at pages 21 and 26 and can be derived from the alignment in Figure 3a that those positions that vary among human, rat, and mouse sequences are positions where it is likely that mutations can be made without affecting bioactivity. For instance, it is conceivable that a given residue in human NsG33 can be replaced with the residue used at the same position in the mouse or rat sequence. By way of example, the alignment shows that at the strongly conserved position 5 of SEQ ID NO: 4 (the human sequence) has the amino acid glutamic acid and the mouse and rat sequences contain the amino acid aspartic acid. One skilled in the art would thus understand that a substitution of glutamic acid with aspartic acid would be unlikely to affect bioactivity.

Similarly, at the non-conserved position 27, the human sequence has an alanine residue and the mouse and rat sequences have an aspartic acid residue. Therefore, one skilled in the art would have understood that, at this position, the alanine can be substituted with an aspartic acid residue without affecting bioactivity.

As the alignment in Figure 3a provides four degrees of conservation, fully conserved, strongly conserved, weakly conserved, and non-conserved, even more guidance is given as to which residues can be substituted and how these can be substituted. Thus, one skilled in the art would have understood that a residue marked as strongly conserved, ":", can be substituted with another amino acid residue belonging to the same "conservation group" (see page 21, line 18, and page 26, line 31). For example, S can be substituted with T and A, and so forth. Likewise, it is conceivable that amino acids marked as weakly conserved, ".", can be substituted with other amino acids belonging to the same "weak conservation" group.

Finally, it is taught by the specification (page 21, lines 33-36) that any polypeptide can be assayed for bioactivity, e.g., in the striatal culture assay of Example 15. It is therefore submitted that the inventors were indeed in possession of the genuses of bioactive polypeptides used in the methods defined by claims 92, 132, 134 and 135.

Rejections under 35 U.S.C. § 112, first paragraph, enablement

Applicant notes that the Office acknowledges enablement for treating a definable population of neurons affected in Huntington's disease with a structurally and functionally definable NsG33 polypeptide with recited functional characteristics. Applicant submits that the amended claims fall within the subject-matter acknowledged by the Office to be enabled.

Amended claims 92, 132, 134, and 135 recite a definable population of neurons as being striatal neurons. These are the neurons affected in Huntington's disease as provided in the specification. As stated above, instant claims 92, 132, 134, and 135 also provide a structurally definable NsG33, as follows:

In claim 92, the structure is defined as having 95 % sequence identity to SEQ ID NO: 4 and having conserved cysteines at specific positions.

In claim 132, the structure is defined as having 95% sequence identity to SEQ ID NO: 4, and the position and identity of approximately 80% of the amino acids of SEQ ID NO: 4 are defined with reference to Figure 3a.

In claims 134 and 135, the structure is defined as having 95% sequence identity to SEQ ID NO: 4, and to comprise a consensus sequence identified on the basis of the fully conserved residues in Figure 3a.

In all the independent claims, NsG33 is functionally defined as being neurotrophic and the NsG33 treatment has the functional characteristic of providing trophic support to the striatal

neurons as demonstrated in Example 15. Applicant therefore respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 132 recites that the neurotrophic polypeptide comprises all the amino acids marked in Figure 3a as fully conserved. The Office contends that the figure legend does not describe what markings are "fully conserved." Applicant respectfully disagrees and would like to point to the figure legend for Figure 3a (page 8, line 3):

""*"indicates positions which have a single fully conserved residue."

This is a clear indication of which residues are considered fully conserved. For the Office's information, these fully conserved residues are those which are recited in the consensus sequence of instant claim 134.

For claim 133, the Office contends that there is no figure marking indicating which residues are "strongly conserved." The instant claims have specified that residues marked as strongly conserved are marked with an ":" in Figure 3a. In the legend to Figure 3a, on page 8, line 4-5 the marking is given as ":." The specification on page 26, lines 30-31, also recite that a variant preferably "comprises at corresponding positions the residues marked in Figure 3a as strongly conserved (:) strongly conserved groups include:.... "

Withdrawal of the objection is therefore respectfully requested.

The Office further states that the terms fully conserved and strongly conserved are not defined by the claim. The applicant respectfully disagrees. In the instant claims, fully conserved and strongly conserved residues are identified as those residues marked in Figure 3a with "*" and ":" respectively. As the position of the strongly conserved residues is defined with reference to

Figure 3a, the person of skill in the art can easily identify those positions in the human sequence, which are marked by "*" and ":" in the alignment.

The applicant also submits that the term "fully conserved" is known and appreciated by a person skilled in the art to mean a residue which is the same in two or more different sequences at corresponding positions. Again the person of skill in the art can easily identify the positions and the residues in the alignment in Figure 3a.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(b)

The claims remain rejected over Tang et al. The Office states "because Tang specifically teaches the skilled artisan to use the protein identical to SEQ ID NO:4 to 'treat Huntington's" disease patients, as claimed, Tang's teachings are further enabling within its own right; absent evidence to the contrary." Applicant respectfully submits that Tang could not have reasonably enabled one skilled in the art to treat Huntington's disease with the claimed polypeptides.

The facts of the present case are analogous to those considered in Impax Labs., Inc. v. Aventis Pharms. Inc., 545 F.3d 1312 (Fed. Cir. 2008). In Impax, the question was whether a prior art disclosure enabled the use of riluzole to treat amyotrophic lateral sclerosis (ALS), thus anticipating the patent at issue. The prior art reference taught a generic formula for compounds that could be useful for treating conditions associated with the effects of glutamate, including ALS. (See U.S. Patent No. 5,236,940). The prior art reference also specifically taught that riluzole fell within the generic formula. However, nowhere did the prior art specifically teach the use of riluzole for the treatment of ALS. The court considered whether "excessive experimentation would have been necessary to practice the invention." (Id. at 1315). The court found that "formula I of the alleged prior art discloses hundreds or thousands of compounds and several diseases. Moreover, nothing in the [prior art reference] would direct one skilled in the art to recognize that riluzole could be

used to treat ALS." (Id). Further, the court "rejected the notion that the mere mention of riluzole is sufficient to put one skilled in the art in the possession of the invention." (Id.). Finally, the court found that none of the dosing information disclosed in the prior art was specific for riluzole and that there were no working examples involving riluzole. (Id.). Based on these findings, the court concluded that "one of ordinary skill in the arts would have needed extensive experimentation to link riluzole with the treatment of ALS"; thus, the reference was not anticipatory. (Id at 1315 and 1316).

The facts of the present case are similar to those outlined in Impax. Tang discloses over 2000 unrelated amino acid sequences. Tang also asserts that these amino acids may be useful to treat nearly every conceivable disease, including diseases where tissue regeneration is desirable (e.g., neurological diseases, neural trauma, and ligament repair) (Tang, pg. 25); diseases where it is desirable to administer a compound with "immune stimulating or suppressing activity," including a long list of immunological disorders (pg. 47); infertility (pg. 51); cancer, including a long list of cancer types (pg. 53); and "other activities," including the treatment of infections, enhancing body characteristics, biorhythms, and analgesic effects (pg. 61). In short, Tang speculated that some of the over 2000 proteins identified might be useful in treating any one or more known diseases or conditions. Tang does not provide any guidance as to which proteins would be useful for the treatment of any particular disease or disease generally.

Thus, similar to the prior art reference in Impax, Tang discloses "hundreds or thousands of compounds." Also, similar to the disclosure of riluzole in Impax, Tang discloses the specifically claimed compound. However, while the prior art reference of Impax disclosed a series of structurally related compounds (i.e., they all shared a common generic formula), the thousands of proteins of Tang are unrelated. Furthermore, while the prior art document in Impax disclosed several, related, neurological disorders to be treated by the genus of disclosed compounds, Tang discloses a long list of nearly every conceivable disease, including diseases with opposing mechanisms of action (e.g., immune stimulating or suppressing activity). Finally, similar to Impax,

Tang provides no working examples with the claimed protein, nor does it provide any dosing information specific to the protein.

Based on the analysis provided by the court in Impax, the disclosure of Tang is not sufficient to enable, and thus anticipate, the present invention. The court in Impax found that a prior art reference did not enable the treatment of a specific disease with a specific compound even though the reference taught only a small list of related diseases to be treated with compounds that share a common generic formula. In contrast, Tang teaches a large list of unrelated proteins for the treatment of a much larger list of unrelated diseases and conditions. Given the unrelatedness of the proteins and large number of disclosed diseases, the experimental burden on one skilled in the art to identify the presently claimed protein as a viable treatment for Huntington's disease would have been orders of magnitude greater than that required to identify riluzole as a treatment for ALS based on the reference. Consequently, similar to in Impax, "an ordinarily skilled artisan would have needed to experiment unduly to gain possession of the invention." In view of the above, Applicant respectfully requests that the rejection for anticipation be withdrawn.

Applicant believes the claims are in condition for allowance and such action is respectfully requested. Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2095, under Order No. 50721-006002 from which the undersigned is authorized to draw.

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Respectfully submitted,

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